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THE LOCALIZATION OF STREPTOCOCCI IN THE EYE*

A STUDY OF EXPERIMENTAL IRIDOCYCLITIS IN RABBITS

Ernest E. Irons, E. V. L. Brown, and W. H. Nadler

From the Memorial Institute for Infectious Diseases and the Cook County Hospital, Chicago

The tendency of organisms to invade special tissues of the body is one of the fundamental facts in the etiology and pathology of disease. In the case of some organisms this tendency is the rule, so that the meningococcus usually localizes in meninges, the pneumococcus in the lung, the gonococcus in joints and tendon sheaths, tho at the onset each is present in the blood stream.

Other common pathogenic bacteria, such as the streptococcus, show a more diverse and less constant localization, and while there are in some instances distinguishable differences in cultural characteristics between types and races of streptococci producing different lesions, in many cases streptococci isolated from various sites, and giving rise to varying clinical pictures, show no such cultural or morphologic differences. It has been repeatedly pointed out that the peculiarities of various organs and tissues as regards blood supply, trauma of use, and the special requirements of the invading organism with respect to protection from unfavorable influences, food supply, and oxygen tension, probably have much to do with determining the localization of subsequent generations of the organism.

Organisms long resident in some focus in the body, such as the tonsils, may spontaneously and suddenly invade other tissues, and set up new processes, which present clinical pictures entirely different from those produced before; organisms from these new lesions may cause similar lesions in animals. Rosenow found that streptococci isolated from the tonsils and from the wall of the appendix in patients suffering from appendicitis produced appendicitis in rabbits; that streptococci from patients suffering from arthritis produced a large proportion of joint lesions; and that streptococci from cholecystitis produced cholecystitis in animals after intravenous injection. As a rule, these peculiar qualities of localization were lost early, sometimes within a very few days after isolation. Occasionally during a series of animal passages, the tendency of an organism to localize in one organ or type of tissue changed so that localizations became more frequent in other organs.

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Streptococcal infections of extremities, such as a subungual infection of finger or toe, have been observed to give rise to a general invasion of the body, with arthritis conforming in clinical type not to that of an ordinary streptococcal sepsis, but to that of a typical attack of acute rheumatic fever.

Of the finer mechanism by which organisms acquire for brief periods this invasive power for special organs or tissues we know little, but the recognition that organisms may take on such new qualities offers an attractive explanation of many hitherto obscure phenomena in disease.

The brief duration of this new localization, frequently the relative insignificance in point of size and clinical manifestations of the original focus which harbored the invader, and the relatively slight systemic disturbance accompanying the event until the development of symptoms in the organs newly invaded, have obscured the relation between the disease and its original focus.

The metastatic origin of lesions of the eye, such as panophthalmitis in streptococcal or pneumococcal sepsis, has long been clearly recognized, and the metastatic origin of similar or less severe lesions of the eye in patients in whom the other symptoms of bacterial invasion are slight or absent, or confined to some focus elsewhere in the body, is now being recognized in an increasing proportion of cases. The argument for the bacterial origin of such lesions of the eye is strengthened by the occurrence in some patients of a preceding or coincident arthritis, in the course of which the presence of bacteria can be demonstrated in the joints, and sometimes in the blood. Stock and others have produced iridocyclitis in animals by intravenous injections of bacteria. Recently Rosenow[1] has noted iridocyclitis in a number of animals, chiefly rabbits, following the intravenous injection of streptococci and other organisms derived from various lesions in man and in animals.

While we believe with Rosenow that the localization of organisms (streptococci) in the eyes (uveal tract) of rabbits in his experiments probably was due in large part to peculiarities of the organisms themselves, we recognize the justice of the argument of those who would maintain that on the theory of probabilities, bacterial embolism of vessels of the eye may be expected in a certain proportion of animals in which large amounts of organisms are introduced by intravenous injection. It might further be urged in support of this accident theory that in the same animals in which lesions of the eye occurred, Rosenow found lesions of other organs (of 48 animals showing eye lesions, 28 showed arthritis, 5 hemorrhages in the appendix, 8 ulcer of the stomach, 10 lesions of the endocardium, 8 of the pericardium, 19 of the muscles and the fascia, and 12 of the kidneys), indicating a widespread bacterial invasion. Furthermore, these animals were individuals selected from several hundred similarly inoculated animals.

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[1] Jour. Infect. Dis., 1915, 17, p. 403.

If, however, as Rosenow points out, the sources of the cultures used for these injections are considered, it appears that lesions of the eye were often observed in animals which received cultures of organisms derived from patients suffering from arthritis, myositis, etc., and rarely in animals which were injected with cultures from appendicitis, ulcer of the stomach, or cholecystitis. The source of the cultures therefore seems to have been an important factor in determining the percentage of lesions of the eyes following intravenous injection.

The following experiments were made with the idea of tracing the changes in the power of an organism (streptococcus) which had already given rise to iridocyclitis in a patient, to produce similar lesions in animals after varying periods of residence in the original host, of residence in animal tissues, and of growth on culture media. The accessibility of lesions of the eye to observation greatly facilitates studies of this sort. The exact time of the appearance of the lesions and their course can be more readily noted than when the lesions are in joints or other organs. Minor lesions which might escape notice, or disappear before the death of the animal when they involve joints or internal organs, are more easily detected in the eye.

The patient, J. S., aged 40, a waiter, single, white, was admitted to the Cook County Hospital, April 19, 1915. Eight days before, the patient had "caught cold" and his left tear sac had become swollen. Three days before, it had been opened at a neighboring dispensary. There had been pain in the left side of the head from onset of the eye trouble.

Following an operation upon his nose 20 years before, for the relief of some suppurative process involving the septum, the left eye had "watered" for years, and he had thenceforth been able to "press pus" out of the corner of his eye for 2 or 3 days at a time, at intervals of 5 or 6 months. The sac region had never been swollen and tender until 8 days before admission. About 12 days before admission, an eruption had appeared in an irregular band in the region of the right 9th and 10th ribs (herpes zoster). This had not been accompanied by any marked systemic disturbance. Aside from these lesions, and measles, whooping cough, and mumps in childhood, the patient had suffered no severe illnesses. He had had gonorrhea 12 years before, which had healed without observed complications. He denied syphilitic infection. One brother had died of tuberculosis; 4 sisters and 1 brother were living and well.

The patient was a moderate smoker of tobacco, and took alcoholics freely at times. His general health was good, appetite fair, bowels constipated on admission, urination free.

He was well-developed. Scalp, skull, and ears, appeared normal. The nose showed an old scar over the bridge; the septum was short and the end of the nose depressed. The tongue was coated, the tonsils enlarged, showing some hyperemia. The teeth were carious; radiographs showed 3 alveolar abscesses. The affected roots were extracted (Dr. Puterbaugh). The sinuses on admission were normal clinically (Dr. Friedberg), and radiographs showed normal densities (Dr. Blaine). Later the left antrum filled with pus by direct extension from the tear sac following an operation.

A number of healing lesions of the skin extended in a band around the chest from midsternum to the spine on the right side at the level of the 8th to the 10th ribs (herpes zoster). Lungs, heart, abdominal viscera, and reflexes, appeared normal. The toes of the left foot were deformed (old injury). There were no other joint lesions. The prostate was moderately enlarged, of uniform consistence, and not hard or tender.

Throughout the course of illness there was little constitutional disturbance and the temperature did not rise above 99.2 F.

Wassermann and gonococcal complement-fixation tests were negative. The urine was normal. Tuberculin tests, made after subsidence of the iritis, were negative after 1 and 4 milligrams subcutaneously.

Blood cultures on April 28 (17 days after onset of iritis) and on May 28, made on plates, in tall dextrose-agar tubes, and in ascites dextrose broth, gave no growth.

Cultures from the tear sac, April 28, contained many streptococci and a few colonies of a white staphylococcus. The streptococcus grew in long chains, produced a wide zone of hemolysis, fermented dextrose, lactose, saccharose, and salicin, but not raffinose, mannite, or inulin. Cultures from the tear sac on 6 subsequent occasions gave approximately the same relative numbers of streptococci and staphylococci.

Smears from the tonsils showed streptococci with a smaller number of gram-negative diplococci. This streptococcus (S. viridans) produced small green non-hemolytic colonies on blood agar. Dextrose, saccharose, lactose, and raffinose were fermented, but not salicin, mannite, or inulin. Two rabbits injected intravenously with cultures direct from the tonsils, developed no lesions of the eyes. One rabbit showed a flaccid paralysis of the hind legs within 2 hours after injection and died the following day. There was a large infarct of the lung with multiple small infarcts and subpleural hemorrhages, 2 small subendocardial hemorrhages, and injection of the vessels of the pia with multiple hemorrhages almost continuous in the lower half of the cord. The second rabbit survived for 3 weeks without symptoms. No anatomic cause of death was found; a gram-positive bacillus was isolated from the heart blood.

The region of the left tear sac was much swollen, the skin over it red, tense, and tender. Large quantities of pus could be expressed. The left eye showed marked ciliary and conjunctival injection. A long narrow slightly raised epithelial vesicle ran along the entire margin of the upper inner corneal limbus; a shorter one lay just inside the lower outer limbus. The stroma beneath was distinctly furrowed out. Temporal to the upper furrow the marginal stroma was superficially vascularized for a width of 1 mm. along the limbus between 12 and 2:30 o'clock. The cornea was otherwise clear. The iris had a greenish discoloration (fellow iris, blue). The pupil dilated ad maximum up and in, less well upward and outward, and least well down and inward.

Posterior synechiae involving all layers of the iris were found at 8 and 5 o'clock, and the pupillary border was straight from 3 to 6 o'clock. There was no definite pupillary exudate, but the disc was seen hazily.

The conjunctiva of the right eye was somewhat injected, the pupil round, regular in outline, reacting to light and accommodation.

Three weeks after admission the acute swelling of the tear sac had subsided and it was fully opened and drained May 7 (Dr. Clark). No necrosis of bone was found. In the 5th week the tear sac was again opened and drainage into the nose effected. Some necrotic bone in the region of the ethmoid cells was found and curetted May 25. The center of the nasal quadrant of the cornea now showed a yellowish-white dot of infiltration, located in the anterior stroma and measuring only ⅓ mm. in diameter. In the course of the next few days 3 or 4 other areas appeared nearby. At first they were merely vesicles; then they broke and tiny areas of gray infiltration appeared beneath the pitted surface. The limbic vesicles also collapsed on the furrowed-out stroma and all gradually healed, very much as phlyctenulae do. Ciliary injection and conjunctival chemosis were marked. The pupil dilated well, but the iris remained greenish, considerably swollen, with markings blurred. Brown dots of detached iris pigment were found on the lens capsule.

In the 8th week the adjoining antrum, previously free of infection so far as could be determined clinically and by transillumination and radiographs, was found full of pus and connected directly with the tear sac. The antrum was drained through the nose. Bloody pus was obtained by lavage (Dr. Friedberg). In the 12th week the pus disappeared from both the tear sac and the antrum; the iritis was relieved and did not return in 10 weeks of subsequent observation.

THE PRODUCTION OF IRIDOCYCLITIS IN ANIMALS

Cultures taken from the tear sac of the patient, after varying periods of growth on laboratory media, were injected intravenously into rabbits. For convenience of discussion, the animals have been divided into 7 series, each series including the animals inoculated with cultures taken from the patient on the date indicated. The series therefore afford opportunity of studying changes in the invasive power of the streptococcus with respect to the eye and other organs of rabbits after varying periods of residence in the human body.

SERIES I

Four rabbits were injected intravenously with suspensions in salt solution of the 3rd and 4th subcultures on human-blood agar of a hemolytic streptococcus isolated from the tear sac of the patient on April 28. Iritis appeared in 3 of these rabbits (Rabbits 1, 3, 4).

Rabbit 1.—May 15, injected intravenously with a suspension from one 24-hour blood-agar slant (3rd subculture) of a hemolytic streptococcus from the tear sac of the patient.

May 19.—Right eye red, watery, with distinct conjunctivitis; vessels injected. Anterior chamber clouded. Dark iris, of darker color than normal left. Iris thrown into radial folds. Exudate adherent to anterior surface of iris, floating over pupil, appearing as tho squeezed from a narrow tube.

May 20.—Animal killed. No streptococci obtained in cultures from aqueous. Sections, however, disclosed many streptococci. Hemolytic streptococci in cultures from heart blood. No gross lesions of viscera.

Rabbit 3.—May 19, intravenously injected with a suspension of a culture from a 24-hour blood-agar-slant transfer from the culture used for Rabbit 1.

May 20.—Eyes unchanged.

May 22.—Severe inflammation in left eye, with conjunctival hemorrhages, ciliary injection, and hypopyon. Iris appeared yellow and covered with exudate. Right eye normal. Rabbit killed with ether. Hemolytic streptococci in cultures from purulent content of anterior chamber. Streptococci in cultures from joint. Heart blood sterile.

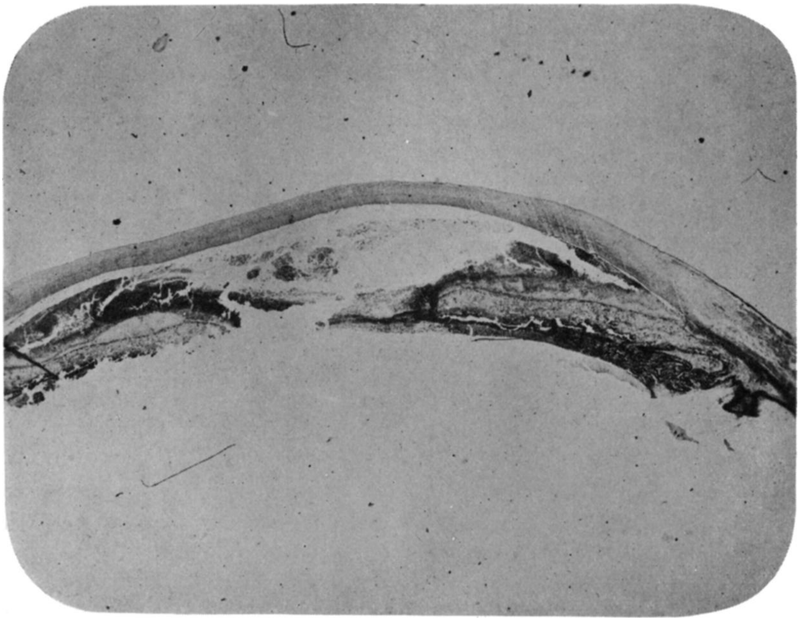

Fig. 1. Severe suppurative iridocyclitis in Rabbit 3. Note the exudate in the anterior chamber, and the swollen infiltrated iris and ciliary body, 3 days after intravenous injection of streptococci from the patient. × 10.

Rabbit 4.—May 19, intravenously injected with a suspension of one-half blood-agar-slant transfer from the culture used for Rabbit 1.

May 20.—Eyes unchanged.

May 21.—Alive but condition not recorded.

May 22.—Found dead. Left eye showed conjunctival hemorrhage; limbal vessels were injected; palpebral conjunctiva red, hemorrhagic. Iris not satisfactorily examined because of clouded cornea. The clinical observations of this animal were hardly sufficient for a diagnosis of iridocyclitis. Sections, however, showed lesion of the ciliary body, with many streptococci in the tissue of the corona ciliaris. Right eye normal. Streptococci in culture from knee joints. A small subendocardial hemorrhage; valves normal. No other gross visceral lesions. No herpes.

A suspension of fluid containing streptococci from the eye of Rabbit 3 was injected intravenously into Rabbit 7. No changes were observed in the eyes and the animal was discharged apparently well 26 days later. The number of streptococci injected was necessarily small. Pure cultures of streptococci from the eye of Rabbit 3 (suspended in salt solution, the amount being equivalent to 3 c.c. of an 18-hour culture in ascites dextrose broth) were injected intravenously into Rabbits 8 and 9. No ocular lesions were produced.

SERIES II

The cultures used in this series were isolated from the patient May 24. At this time the iritis was worse than it had been for some days previously, and there was severe inflammation in the tear sac.

Four rabbits (10, 11, 12, 13) were injected with suspensions of 20-hour ascites-dextrose-broth cultures inoculated directly from the patient. These cultures contained a small number of staphylococci in addition to the predominating streptococci. Rabbit 11 died 4 days later without evidence of iritis. There were no clearly marked focal lesions in the viscera; cultures from the heart blood and from the joints showed streptococci. Rabbit 13 showed no iritis for 4 days; was found dead on the fifth day. The media of the left eye were more cloudy than usual, but stained sections showed no evidence of iritis. There was a large pulmonary infarct. Rabbits 10 and 12 developed definite iritis.

Rabbit 10.—May 25, received a suspension of organisms from 5 c.c. of an ascites-dextrose-broth culture. After 24 hours, conjunctivitis developed in the right eye. Iris dull diffuse red in color. Four hours later conjunctivitis more marked, with edema of lids and lacrimation; ciliary injection; "iris covered with spots of exudate"; the color of the iris at this time, more gray-yellow. At 28 hours, the aqueous was clouded. Left eye normal. Animal lively. At 48 hours there were severe conjunctivitis, ciliary injection, chemosis. Iris beaded with exudate, the pupil partly obliterated by a circular gray-white exudate adherent to the iris margin. Spontaneous perforation occurred at the corneal margin, and death 52 hours after inoculation. The exudate from the anterior chamber contained gram-positive cocci in chains; hemolytic streptococci were shown in cultures from the anterior chamber, from the heart blood and from the knee joint. No herpes; no gross changes in muscles, appendix, intestine, liver, spleen, or kidney. In the lungs some edema. Several small hemorrhages in the stomach. One small subendocardial hemorrhage in the right auricle; the valves normal.

Rabbit 26.—May 28, received a suspension of streptococci (from 6 c.c. of a 24-hour culture in ascites dextrose broth) isolated from the eye of Rabbit 10. After 24 hours, the left eye showed slight lacrimation, with injection of conjunctival vessels, marked ciliary injection, and cloudy aqueous. The cornea perforated spontaneously 72 hours after inoculation, and the animal was found dead on the 4th day. Streptococci shown in cultures from aqueous, heart blood, and knee joint. No significant visceral lesions were found.

Rabbit 26a.—Inoculated with a smaller amount of the same culture that Rabbit 26 had received, died on the 4th day. No lesions of the eyes or of the viscera found. Streptococci shown in the heart blood.

Streptococci from 2 c.c. of an 18-hour ascites-dextrose-broth culture from the eye of Rabbit 26 were injected intravenously into 4 rabbits (40, 41, 42, 43). One animal died after 4 days. Cultures from the heart blood showed no streptococci. The other 3 rabbits were discharged well after 14 days.

Streptococci from the heart blood of Rabbit 26 injected into 2 rabbits (37, 38) produced no definite lesions of the eyes. In one animal (37), dead on the 6th day, the vessels of the left nictitating membrane were more prominent (probably a result of the position of the animal after death). The joint fluid was cloudy; the colon bacillus was isolated. No streptococci were found in the heart blood. Rabbit 38 developed severe arthritis but survived. It was killed with chloroform 8 weeks after inoculation. Cultures from heart blood and joints remained sterile. There were no visceral lesions except moderate coccidiosis of the liver.

Rabbit 12.—Received a suspension of streptococci from 5 c.c. of a 20-hour ascites-dextrose-broth culture on May 25. After 48 hours the eyes appeared normal, but after 72 hours the left eye was inflamed with marked conjunctivitis, chemosis, and lacrimation. The iris (normally brown) appeared hazy, gray-yellow in color, with an adherent exudate. Hypopyon, with perforation, was followed by ocular hemorrhage and the death of the animal on the 5th day.

There were found a few small hemorrhages in the mucosa of the stomach, and a subendocardial hemorrhage 2 mm. in diameter in the right auricle. No other gross visceral lesions.

Cultures from within the left eye showed hemolytic streptococci. Streptococci were shown in cultures from the heart blood. Sections showed inflammation of the ciliary body, with exudate and masses of streptococci in the anterior chamber.

Four rabbits (33, 34, 35, 36) received suspensions of a pure culture of a hemolytic streptococcus from the eye of Rabbit 12.

Rabbit 36.—The left conjunctiva was injected and there was some lacrimation 24 hours after injection. The animal was found dead on the second day. The anterior chamber was cloudy (possibly postmortem change). Cultures from the heart blood and from the left knee joint showed streptococci.

Rabbits 33, 34 and 35.—Died after 1, 7, and 16 days; streptococci were shown in cultures from the heart blood of 33 and 34, and from the knee joint of 33. There were no ocular lesions.

Rabbits 16 and 17.—Injected with a 3rd transfer in culture from the patient; showed no lesions of the eyes.

SERIES III

Cultures taken May 26 from the tear sac of the patient, after curettage and packing 4 hours previously, contained hemolytic streptococci and a few staphylococci. To avoid as far as possible changes in the organisms during the period of subculture, the original broth cultures containing staphylococci, together with streptococci, were centrifugated and the animals injected with sedimented organisms within 24 hours after removal from the patient.

Two rabbits (18, 19) died after 12 and 11 days. There were no ocular lesions.

SERIES IV

Cultures taken May 28 from the tear sac were similar to those of Series III.

Two rabbits (30,31) died after 3 and 15 days. There were no ocular lesions. Streptococci were found in the joint of Rabbit 30.

SERIES V

Cultures taken June 2 from the tear sac contained chiefly hemolytic streptococci, with a few staphylococci.

Four rabbits (44, 45, 46, 47) were injected with pure cultures of the streptococci. Two survived without lesions of the eyes (49, 50). In Rabbit 51, there was no visible lesion of the eye on the 2nd day; on the 3rd day the animal was found dead. The conjunctiva of the left eye was moderately injected, with some exudate, but there was no clearly defined lesion of the bulb (probably a postmortem change or due to terminal struggles). Sections showed no lesions of the uveal tract. Cultures from the turbid joint fluid contained streptococci. Rabbit 48 died on the 15th day without ocular lesions.

SERIES VI

Cultures from the tear sac, June 7, showed an almost pure culture of a hemolytic streptococcus.

Six rabbits (55-60) injected with these cultures developed no lesions of the eye.

SERIES VII

Cultures from the tear sac, June 16, yielded streptococci and a few staphylococci.

Four rabbits (81-84) were injected with doses corresponding as nearly as possible to those given to the rabbits in Series II. Three of the 4 succumbed within 3 days, and hemolytic streptococci were isolated from the heart blood of each. The virulence of the streptococcus for rabbits seemed not appreciably decreased, but no definite lesions of the eyes were produced. A transient conjunctivitis with discharge was noted in the left eye of Rabbit 81, but such slight lesions were occasionally noted in uninoculated animals.

ANATOMIC STUDY OF THE RABBITS' EYES

As noted, 4 rabbits were injected intravenously with the pure cultures of the hemolytic streptococcus obtained from the acutely inflamed tear sac of the patient on April 28, 1915; 3 of these rabbits developed iritis. Similarly, 2 of 4 rabbits gave positive results with material obtained 26 days later (Series II). Four of these animals showed clinical and anatomic suppurative iridocyclitis; in Rabbit 4 the lesion did not reach the suppurative stage before the death of the animal. The streptococcus was found inside all the affected eyes and not in the fellow eyes.

Rabbit 3 of the first series was typical.

On section the episclera was found much infiltrated and the sclera at the sulcus permeated by cells through all layers. The corneal epithelium was absent for the most part and where present at all, was reduced to 1 or 2 layers. The anterior two-thirds of the stroma was moderately infiltrated with leukocytes; the posterior third was necrotic. Descemet's membrane was everywhere denuded of its endothelium. The iris and the ciliary body were much swollen and densely infiltrated with cells and fibrin. This exudate was breaking through the ciliary processes and the posterior layers of the iris, filling out the posterior chamber, throwing the ciliary processes forward, matting them together, and binding both the corona and the iris to the lens capsule, blocking the pupil completely and extending over the iris through the lateral thirds of the anterior chamber. The central pupillary third of the anterior chamber

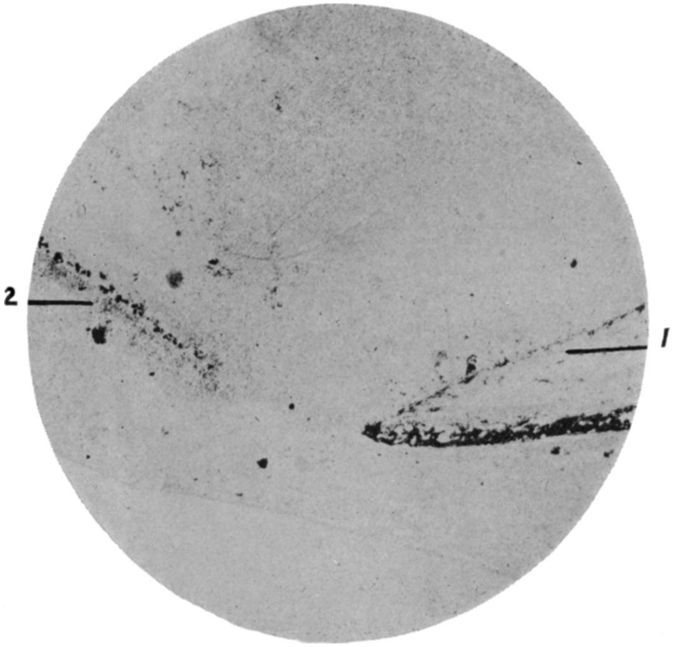

Fig. 2. Early stage of iridocyclitis in Rabbit 1, killed 5 days after inoculation. 1 = anterior surface of the iris. 2 = line of leukocytes in the pupillary area full of streptococci. × 60.

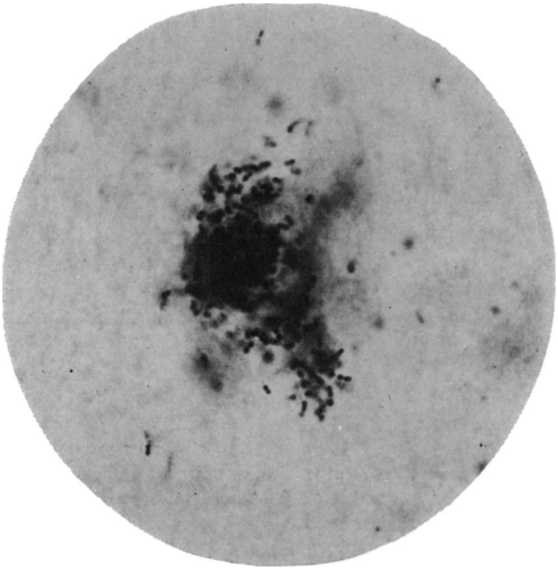

Fig. 3. Leukocyte (from the line of cells lying across the pupillary space in Fig. 2) filled with streptococci. × 1200.

was occupied by a fibrin clot. The spaces of Fontana were distended and the posterior end of Descemet's membrane was separated from the stroma by leukocytes. The exudate continued back behind the root of the iris between the ciliary body and the sclera to the beginning of the chorioidea. The chorioidea itself was little invaded and the retina not at all.

The process was therefore a severe suppurative iridocylitis. A similar but less severe iridocyclitis was found in Rabbit 1. It evidently represented an earlier stage of the process; the disposition of the organisms in the tissues could be better studied than in the severer type.

There was a sharp line of demarkation between the fibrinous clot occupying the central third of the anterior chamber and the cellular exudate which lay over the iris on each side of the pupil. Between the two was an almost unbroken row of leukocytic clumps, so filled with organisms that in Gram-Weigert sections they made a blue line running from the pupillary border to a point half way between the center and the base of the cornea on each side. In front of the line the fibrin clot was almost, if not entirely, devoid of cocci, but behind it the exudate was everywhere richly permeated with chains and groups of streptococci. The iris itself was only moderately infiltrated, much less so than the ciliary processes, and no organisms were found in the iris. Other sections showed 2 fairly large abscesses in the posterior portion of the ciliary body, just external to the line of the bases of the processes. The abscesses contained no visible organisms. The exudate between the ciliary processes contained large numbers of cocci, yet they were much less numerous than in front of the iris. In contrast to conditions found in the iris numerous organisms could be found within the stroma of the ciliary processes, about the vessels, among the infiltrating cells, and between the cells making up the layers of its unpigmented and pigmented epithelium. No organisms could be found in the infiltrate blocking the spaces of Fontana and the ligamentum pectinatum, or lying outside the ciliary body. The origin of the great mass of both the leukocytes and the organisms, therefore, seemed to be in the ciliary body rather than in the iris.

Rabbit 4 showed the earlier changes produced by the invading organism.

Some sections showed a fibrin clot and a large leukocytic node in one sinus angle. This mass of leukocytes could be followed well back through the ciliary body in successive sections to the posterior end of the corona ciliaris, where it formed a node about a vein (Fig. 5). Gram-Weigert stains showed many chains and clumps of streptococci free in tissue spaces throughout the ciliary body. (Figs. 6 and 7.)

Rabbit 12 of the second series showed a more extensive suppurative process, with rupture of the sclera clinically.

On section a broad gaping rupture was found near the posterior end of the ciliary body on one side, with hemorrhage and prolapse of the detached retina part way into the wound. The iris and ciliary body showed very extensive infiltration, and the pupil and both chambers were choc-a-bloc with fibrin

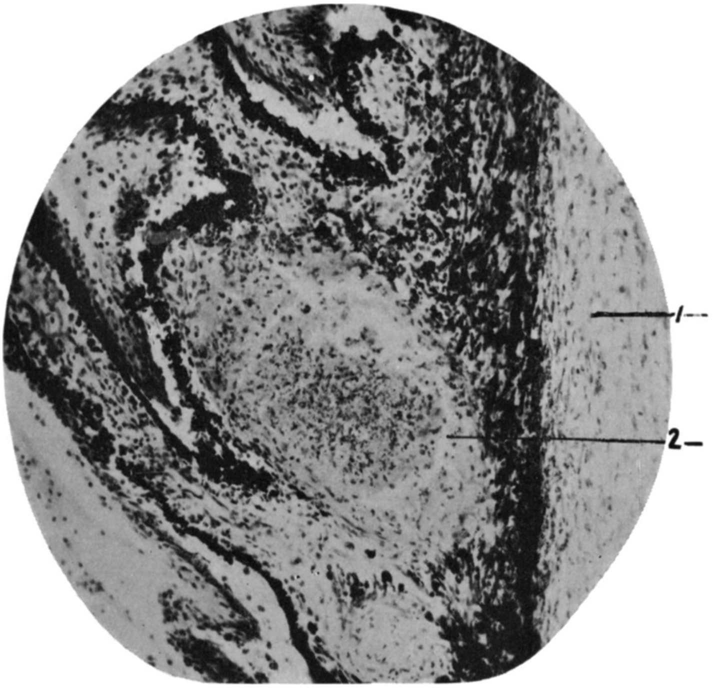

Fig. 4. Abscess in the posterior part of the ciliary body in Rabbit 1. 1 = sclera. 2 = ciliary body with abscess. × 140.

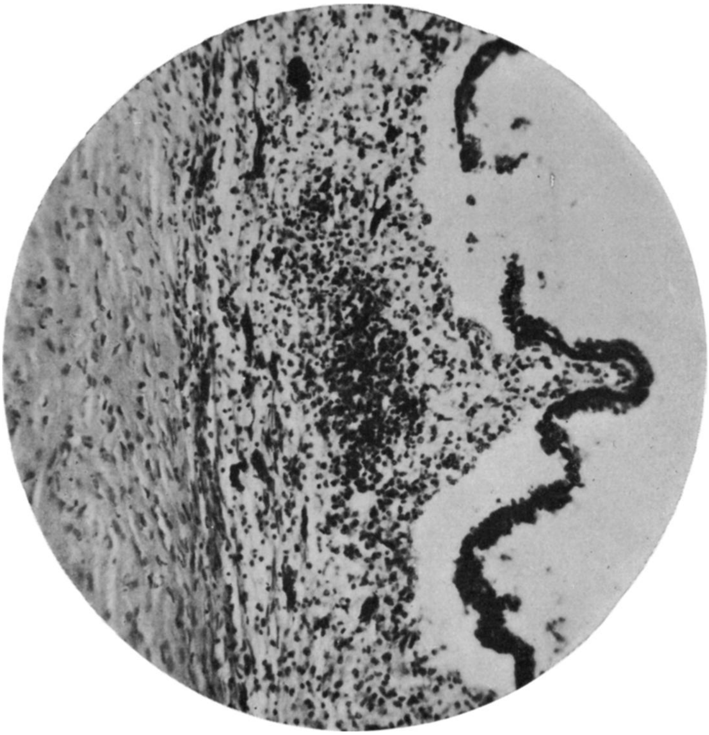

Fig. 5. Node from the infiltration about a vein in the posterior part of the ciliary body. × 170.

and a dense leukocytic exudate. The iris and the ciliary body were similar in appearance to those of Rabbit 3. The marginal thirds of the cornea were swollen to twice the normal thickness. There were an almost complete loss of corneal epithelium and considerable infiltration of the anterior third of the stroma. The region of the ligamentum pectinatum and of the canal of Schlemm showed a massive infiltration, extending half way back to the ora and detaching the ciliary body from the sclera. The iris was bound to the lens on one side by flat synechiae and by synechia of the pupillary border on the other side. The body of the iris on this side was thrown forward, its root adherent to the base of the cornea. The retina and chorioidea were both normal.

Rabbit 10 showed essentially the same anatomic findings. Rabbit 26 (inoculated with pure cultures obtained from the aqueous of Rabbit 10) showed a clinical suppurative iridocyclitis. Most of the eye was sacrificed for cultural purposes, but the organisms were found in sections of the uveal exudate.

Sections from the eyes of 20 other injected rabbits in which there were no clinical evidences of ocular inflammation were carefully examined for inflammatory lesions and bacteria, with negative results.

SUMMARY OF SERIES I TO VII

Hemolytic streptococci isolated from the tear sac of the patient, April 28, during a period of acute iridocyclitis produced iridocyclitis with later hypopyon and perforation of the bulb in 2 of 4 rabbits, and a less marked lesion in Rabbit 4 (Series I). These cultures were from the 3rd and 4th transfers on blood-agar slants. Cultures taken from the tear sac on May 24 during a period of exacerbation of the inflammation in the eye and the tear sac produced iridocyclitis in 2 of 4 rabbits. Cultures of hemolytic streptococci taken from the tear sac on 5 subsequent occasions (May 26 to June 16), during a period of continued improvement in the condition of the eye and the tear sac of the patient, produced no lesions of the eye in a total of 22 rabbits. These cultures were inoculated either from the 1st transfer from the patient (in this case staphylococci were sometimes present), or from the 2nd transfer in pure culture after isolation on blood-agar plates.

The failure of the later cultures from the patient to produce iridocyclitis in rabbits, did not seem to be associated with an appreciable decrease in virulence for rabbits. When equivalent quantities of streptococci were inoculated, animals in the later series died in about the same time as those of the earlier series, and hemolytic streptococci were isolated usually from the heart blood, and frequently from the

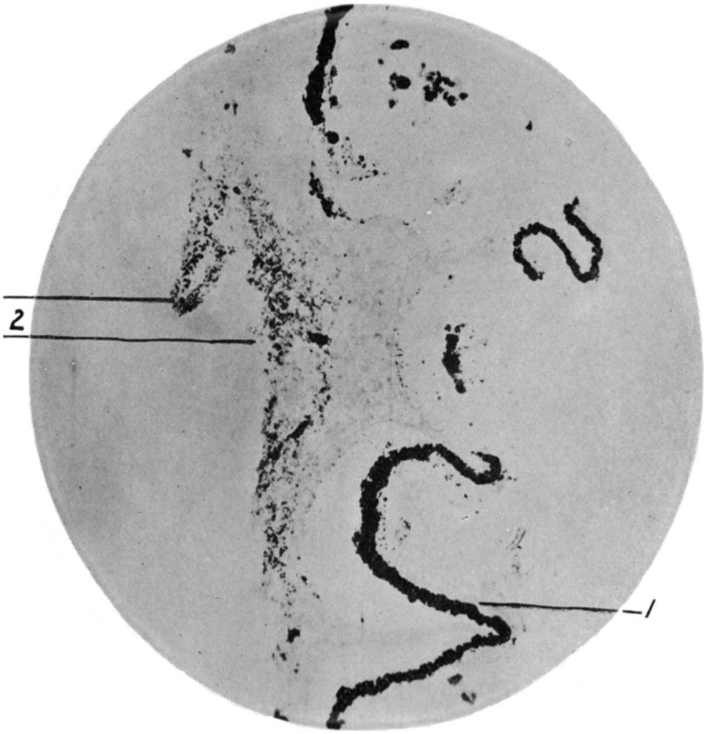

Fig. 6. Masses of the streptococci in the ciliary body in Rabbit 4. 1 = pigment epithelium of the ciliary body. 2 = stained masses of organisms in the loose structure of the ciliary body. Gram-Weigert. × 170.

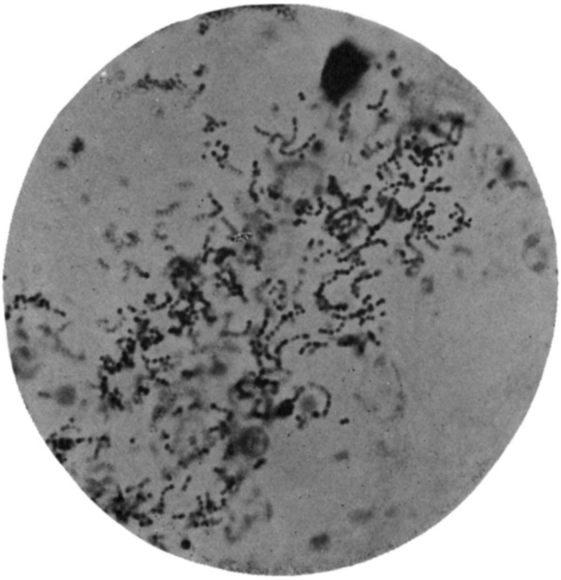

Fig. 7. Streptococci from the area marked "2" in Fig. 6 (Rabbit 4). × 1200.

joints. Other gross visceral lesions were not frequent, tho small hemorrhages in the endocardium, pleura, stomach, and infarcts of the lung, were occasionally noted.

Cultures which had produced ocular lesions in rabbits, and had then been kept in the incubator for 10 days (2 subcultures) no longer produced these lesions. The strain which had produced iridocyclitis in Rabbits 1 and 3 was kept at 37 C. for a few days, and then placed in the ice box. July 7 (52 days after isolation) subcultures no longer produced ocular lesions in rabbits.

Attempts were made to produce lesions of the eye from rabbit to rabbit either by direct transfer of the exudate from the eye or by means of one intervening subculture. Thus, cultures of the streptococcus from the eye of Rabbit 10, in which iridocyclitis had been produced by intravenous inoculations, were injected intravenously into Rabbit 26. Iridocyclitis was produced in this animal and hemolytic streptococci were isolated from the eye and from the heart blood, but inoculations of these cultures in turn in 6 more rabbits failed to produce any further iritis.

The power of the hemolytic streptococcus in these experiments, to localize in the eye and produce iridocyclitis in rabbits was lost in a relatively short time (1) in the body of the original host (tear sac), (2) in cultures, and (3) during animal passage. This change in tissue localization seemed not to be associated with any demonstrable decrease in lethal power.

The hemolytic properties and fermentative reactions in various sugar media of the streptococci from the tear sac were studied from time to time after growth on culture media and after successive passages through animals. The zone of hemolysis on blood-agar plates became somewhat smaller after 2 months growth on culture media (blood agar). After 6 months the 11th subculture showed no further decrease in the zone of hemolysis. When first isolated, cultures formed acid in media containing dextrose, saccharose, lactose, or salicin, but not in media containing raffinose, mannite, or inulin. In later cultures (2 months), mannite and raffinose were inconstantly fermented. After passage through a rabbit (intraocular injection), the streptococcus, being recovered in pure culture, when placed in sugar media again gave the same reactions as when first isolated from the patient.

The failure of the later cultures to produce lesions in the eyes of rabbits did not appear to be accompanied by any constant alteration in fermentative power. Some decrease in hemolytic power was noted.

THE EFFECT ON STREPTOCOCCI OF RESIDENCE IN THE EYE

The idea that organisms which ordinarily do not localize in a given tissue may be so modified by continued residence and growth in it that they later localize in the unusual site with more or less regularity, is by no means a new one.

Bezançon and Labbé[2] inoculated an animal intravenously with staphylococcus from a cutaneous abscess, and after traumatizing a joint, obtained localization in the joint. Cultures obtained from this joint showed a tendency to localize in joints on subsequent intravenous inoculation into animals, altho this localization could not be maintained in subsequent series of animals. Forssner[3] (1902), working with a streptococcus isolated from an axillary abscess, grew the organism in extracts of kidney and in kidney tissue both in vitro and in vivo. Whereas the original organism showed no tendency to localize in the kidneys on intravenous injection, the strains obtained after passage through kidneys of animals exhibited a remarkable tendency to produce lesions of the kidneys on intravenous injection. This property after being acquired, was retained by the organism for 4 or 5 generations on serum broth after the last animal passage, and then was lost.

Other organisms behave similarly. Strains of B. pestis repeatedly grown in the lung show an increased tendency to produce pneumonic lesions on intravenous, or even subcutaneous, injections.

The experiments of Forssner in which organisms after being grown in a special organ of the body, such as the kidney, acquired the power to localize and produce lesions with increasing frequency in that organ after intravenous injection, suggested the possibility of producing by successive transfers from eye to eye in rabbits a similar localization. It is obvious that the streptococcus from our patient did not acquire its quality of localization through actual previous residence in the tissues of his eye, and even if we admit the possible influence of residence in a contiguous organ (tear duct), this relation could hardly be held to explain the course of events in other cases in which ocular or other metastases originate from primary bacterial lesions in distant parts of the body. Nevertheless, it seemed desirable to find whether an organism which had previously produced iridocyclitis in rabbits could regain this quality of localization by continued growth in the tissues of the eye.

1. The strain of hemolytic streptococcus which had produced ocular lesions in Rabbits 1, 3, and 4, after being kept on blood agar for about 2 months in the ice box, no longer produced lesions of the eye. Cultures

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[2] Compt. rend. Soc. de biol., 1900.

[3] Nord. Med. Ark., 1902, Part 2, No. 4, p. 18.

were inoculated into the anterior chamber of the eye of a rabbit; after 2 days, cultures from the eye were made in ascites dextrose broth, and after 18 to 24 hours' growth in incubator, a portion of this culture was introduced into the eye of a second rabbit. This transfer was repeated for 7 animal passages. After each eye passage the organisms from the broth cultures, centrifugated and suspended in salt solution, were injected intravenously into from 2 to 4 rabbits. In the later transfers cultures from the eye contained in addition to hemolytic streptococci, staphylococci, and still later non-hemolyzing streptococci in large numbers. In order to minimize the period of growth outside the eye in this experiment, the hemolytic streptococci were not isolated in pure culture before injection into the succeeding eye, but the relative proportions of streptococci and staphylococci were determined for each culture inoculated.

No ocular lesions were produced in the 14 rabbits injected during the first 5 eye passages. In cultures from the 6th and 7th animal passages most of the colonies of streptococci no longer produced hemolysis on blood-agar plates. One rabbit (196, injected with cultures from the 7th eye passage) showed some circumcorneal injection of both eyes, but sections showed no lesions of the uveal tract.

From a comparison of the non-hemolyzing streptococcus with pure cultures of the original strain of hemolytic streptococcus we are inclined to think that the decrease in number of hemolytic colonies, and increase in non-hemolytic colonies was due to the introduction during animal passage of a contaminating streptococcus which happened to be non-hemolytic, rather than that the original hemolytic strain underwent any sudden change in characteristics with respect to growth on blood agar.

The animals injected intravenously with cultures from the later eye passages (4th to 7th) showed increasing lesions of the kidney and of the heart muscles (miliary abscesses). Cultures and sections demonstrated, however, that staphylococci and not streptococci were present in these lesions; comparative counts of streptococci and staphylococci in the injected cultures showed an increase in the proportion of staphylococci where abscesses were most numerous.

2. A strain of hemolytic streptococcus taken from the tear sac after subsidence of iritis (Series VII), which had failed to produce lesions of the eye in rabbits when first isolated, was similarly passed through 7 eyes. Hemolytic streptococci disappeared from the cultures

after the 5th eye passage. The streptococci remaining in cultures were uniformly non-hemolytic and otherwise appeared culturally different from the original. Of 10 rabbits receiving hemolytic streptococci after the first 4 eye passages, and 9 rabbits from the later 3 passages, none developed characteristic lesions of the eye. One rabbit injected with cultures from the 7th eye passage showed a slight circumcorneal inflammation for 2 days, but no signs of further intraocular inflammation developed and the animal was discharged after 3 weeks.

3. A laboratory strain of hemolytic streptococcus (from severe tonsillitis) was similarly passed through a series of 7 rabbit eyes, and injected intravenously into rabbits after each of the last 4 passages. Cultures from the 7th eye passage contained both hemolytic streptococci corresponding culturally to the original strain, and non-hemolytic streptococci growing in small dry colonies, resembling those observed in the cultures from later passages of the two preceding series. Pure cultures of both types were injected into rabbits. No ocular lesions were produced in a total of 20 rabbits injected in this series.

The appearance of the non-hemolyzing type of streptococcus in cultures from the later injected eyes, raises the question as to whether this organism was a derivative of the original hemolyzing strain, or was a contamination introduced during animal passage. That opportunities for such contamination were repeatedly present, is evident from the conditions of the experiment, and the appearance of staphylococci in the later cultures. The non-hemolyzing small gray colonies of streptococcus became more numerous in cultures from the later animal passages in all 3 series of rabbits. In 2 of these series strains of streptococci from the tear sac of the patient were used, while in the 3rd series a laboratory culture of a hemolytic streptococcus from tonsillitis was employed, and yet the non-hemolyzing type appeared at about the same time in all 3 series.

The colonies of the non-hemolyzing organisms were smaller and dryer than those of the original hemolytic strains. Raffinose, mannite, and inulin were fermented, as well as dextrose, saccharose, lactose, and salicin, whereas the 3 original hemolytic strains fermented regularly dextrose, saccharose, lactose, and salicin, and only occasionally raffinose, or mannite, over a period of 6 months, both before and after animal passage.

Intraocular injections offer greater opportunities for contamination than intravenous, and so it is hardly fair to compare the appearance of a new type of streptococci in these experiments with the changes reported in cultures of streptococci after animal passage following intravenous inoculation. However, the sudden appearance of the new type of streptococcus in all 3 series of inoculations, which seems in this instance best explained as a contamination derived from the animals, emphasizes the need of care in the interpretation of results, when strikingly new cultural characteristics appear suddenly during animal passage.

SUMMARY

The left eye of a patient suffering from a chronic dacryocystitis became acutely inflamed (iridocyclitis), April 11, coincidently with an acute exacerbation of the inflammation of the tear sac.

Hemolytic streptococci isolated from the tear sac April 28, produced typical iridocyclitis in 3 of 4 rabbits injected intravenously. Hemolytic streptococci isolated from the tear sac May 24, produced iridocyclitis in 2 of 4 rabbits injected. Cultures of hemolytic streptococci from the tear sac taken on May 26, May 28, June 2, June 7, and June 16, failed to produce iridocyclitis in a total of 22 rabbits, whether injected with other organisms from broth culture inoculated directly from the patient, or in pure culture after isolation on blood agar. That the failure of later cultures to produce iritis was not fortuitous, but more probably due to some change in the invasive power of the organism for ocular tissue seems evident from the fact that whereas in the first 2 series, 5 of 8 rabbits injected developed iridocyclitis, in the later 5 series of cultures 22 rabbits showed no such lesions. Furthermore, in the later experiments 24 other rabbits received the same streptococcus either in pure culture or with other organisms, without the production of typical iridocyclitis, such as was observed in the first 5 rabbits. The ability of the cultures to produce lesions of the eye was lost also in transfer from rabbit to rabbit, altho iritis was produced in Rabbit 26 by intravenous injection of the hemolytic streptococcus from the eye of Rabbit 10. This loss of power to produce iritis in rabbits was not accompanied by any demonstrable decrease in virulence for rabbits.

In cultures the quality of localization in the eye was lost after the 3rd or 4th subculture, usually within very few days after isolation. In the case of the first rabbits injected, however, cultures produced iritis 17 days after isolation from the patient.

Attempts to obtain a return of invasive power for tissues of the eye in strains of streptococci which had lost it, by growing the organisms in the living eye, were unsuccessful in one series after passage through 5 animals, and in one series after passage through 7 animals.

These experiments seem to indicate that the invasive power of an organism for special tissue may change within a short period of time during residence in the original host, during animal passage, and in culture, without pronounced or constant changes in cultural characteristics, or in general virulence for animals.